REMARKS

Applicants thank the Examiner for the courtesy of a telephonic interview held on November 30, 2004 with Applicants' attorney, Megan E. Williams.

Claims 35, 36, 38-40, 42-49, 56, 57, and 62-69 are currently pending in the application. Claim 69 has been amended. Claims 35, 36, 38-40, 42-49, 56, 57, and 62-67 have been indicated as allowable. Accordingly, following entry of the amendments presented herein, claims 35-36, 39-40, 43-49, 56-57, and 62-69 will be pending.

No new matter has been added. Support for the amendments presented herein can be found in the specification as filed and/or the claims as previously pending.

Rejection of Claims 68 and 69 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 68 and 69 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description paragraph. Specifically, the Examiner states that

> New claims 68-69 are directed to embodiments of the method of claim 35 wherein minimal structural limits are specified for the "regulatory sequence" comprising a MARE element as specified in claim 35. In claim 68, the regulatory sequence comprises "from about nucleotide -42 to about nucleotide -37 relative to the start site of transcription of +1 of the IL-4 promoter". In claim 69, the regulatory sequence comprises "from about nucleotide -59 to about nucleotide -27 relative to the start site of transcription of+1 of the IL-4 promoter". In making the amendment, applicants' response points to specific portions of pages 47-48 for support. However, there is no literal support at the cited passages from the instant specification, nor from any other part of the originally filed specification, for the very specific limitations recited in the rejected claims for use in the recited methods. Therefore, there is no literal support in the instant specification for the newly claimed subject matter and the rejected claims comprise impermissible new matter.

Applicants respectfully traverse this rejection and submit that the specification teaches the use of regulatory sequences that bind to c-maf, *e.g.*, MARE sequences, in screening assays and that there is literal support for the use of MARE generally, as well as for the specific limitations of claims 68 and 69 in the instant specification.

Pending claim 35, indicated as allowable, is directed to a method for identifying a compound that modulates production of IL-4 in a cell, comprising; providing an indicator composition comprising (i) a c-maf or v-maf protein and (ii) a target DNA comprising a

regulatory sequence of an IL-4 gene which includes a c-maf responsive element (MARE), wherein said indicator composition is an indicator cell or acellular preparation; contacting the indicator composition with each member of a library of test compounds; selecting from the library of test compounds a compound of interest that modulates binding of said maf family protein to said target DNA; and determining the effect of the compound of interest on the production of IL-4 in a cell to thereby identify a compound that modulates production of IL-4. Dependent claims limiting the regulatory sequence of the IL-4 gene which includes a c-maf responsive element (MARE) in claim 35, include: claim 64 (indicated as allowable), in which the regulatory sequence comprises about 3 kb of the upstream regulatory sequences of the IL-4 gene; claim 65 (indicated as allowable), in which the regulatory sequence comprises from about nucleotide -157 to about nucleotide +58 relative to the start site of transcription of +1 of the IL-4 promoter; claim 68, wherein the regulatory sequence comprises from about nucleotide -42 to about nucleotide -37 relative to the start site of transcription of +1 of the IL-4 promoter; and claim 69, wherein the regulatory sequence comprises from about nucleotide -59 to about nucleotide -28 relative to the start site of transcription of +1 of the IL-4 promoter.

The specification teaches assays in which MARE sequences are used. For example, the specification teaches at least at page 36, lines 5-11, that :

> the invention pertains to screening assays for identifying compounds that modulate the activity of a transcription factor that regulates expression of a Th2-associated cytokine gene. In various embodiments, these screening assays can identify, for example, compounds that modulate the expression or functional activity of the transcription factor, proteins that interact with the transcription factor, as well as compounds that modulate these protein-protein interactions, and compounds that modulate the interaction of the transcription factor with a MARE within a Th2-associated cytokine gene.

The specification also teaches at page 39, lines 15-24, that the screening assays of the invention can be used :

> for identifying compounds that modulate the interaction of c-Maf with a MARE in an IL-4 gene regulatory region. Assays are known in the art that detect the interaction of a DNA binding protein with a target DNA sequence (*e.g.*, electrophoretic mobility shift assays, DNAse I footprinting assays and the like; for further descriptions see the Examples). By performing such assays in the presence and absence of test compounds, these assays can be used to identify compounds that modulate (*e.g.*, inhibit or enhance) the interaction of the DNA binding protein with its target DNA sequence. Accordingly, the invention provides a method for identifying a compound that modulates the interaction of a

> c-Maf protein with a maf response element (MARE) of an IL-4 gene regulatory region

The specification also teaches sequences comprising c-maf responsive elements (MARE sequences). Specifically, the specification teaches that examples of MARE sequences were known in the prior art. For example at page 8, lines 9-11, the specification teaches:

> [t]he DNA target sequence to which c-Maf homodimers bind, termed the c-Maf response element (MARE), is a 13 or 14 bp element which contains a core TRE (T-MARE) or CRE (C-MARE) palindrome respectively.

Furthermore, the specification teaches that MARE sequences are found in the regulatory regions of cytokine genes *e.g.*, the IL-4 gene. Specifically, the specification teaches that IL-4 expression can be induced by the proximal promotor region of the IL-4 gene in Th2 cells (Hodge, M. et al. (1995) *J. Immunol.* 154:6397-6405) (page 37, lines 3-5), and that c-Maf specifically binds to MARE sequences in the IL-4 promotor. See, Example 6, page 47, line 7 through page 48 line 36.

With respect to specific MARE sequences in the IL-4 promotor, the specification provides several examples of such sequences. For example, the specification teaches at page 37, lines 8-13, that about 3 kb of the upstream regulatory region of the IL-4 gene can be utilized in the screening assays of the invention. At page 43, lines 17-18 the specification teaches that a reporter construct:

> containing an IL4 promoter fragment from -157 to +68 operatively linked to a chloramphenicol acetyltransferase gene described in Hodge, M. *et al.* ((1995) *J. Immunol.* 154:6397-6405)

can be used to measure c-maf activity.

The specification teaches other examples of MARE sequences. For example, Example 5 and Figure 5A teach that nucleotides -59 to -28 of the IL-4 promotor comprise a MARE and a Th2-specific footprint. Figure 5B graphically depicts MARE sequences within the IL4 promotor, and at page 6, lines 31-37, the specification teaches that

> Figure 5B is a schematic representation of the proximal regulatory region of the murine IL-4 promoter. The top portion shows the primary sequence of the murine IL-4 promoter. The numbers indicated are relative to the start site of transcription at +1. Asterisks denote the Th2-specific hypersensitive residues seen on DNAse I footprint. The bottom portion shows the sequence of the wild type (-59 to -28) oligonucleotide and the 4 bp mutants used in EMSA and the functional assays shown in Figures 6 and 7. Altered nucleotides are shown in lowercase bold and correspond to the numbering system shown in the top portion.

Thus, Figure 5B illustrates a region of the IL-4 promotor which contains a MARE and a Th2-specific footprint (-59 to -28) (as claimed in amended claim 69). The figure also specifically illustrates MARE at positions –42 to –37 relative to the transcription start site of IL-4 (as claimed in claim 68).

In Example 6, utilizing oligos spanning the MARE and the Th2-specific footprint of the IL-4 promotor, EMSA analyses teaches that c-Maf protein binds to both a consensus MARE oligonucleotide and to the 33 bp oligonucleotide containing the NF-AT site and MARE (-59 to –27) (SEQ ID NO.1) (Figure 6). Example 7 teaches that the region which comprises the MARE (nucleotide positions -42 to -37, as claimed in claim 68) and the Th2-specific footprints are essential for IL-4 transcription (see muts 2, 3, and 4).

Furthermore, Example 7 and Figure 7A teaches that the ability of c-Maf to transactivate the IL-4 promoter maps to the MARE and Th-2 specific footprint, the region taught in Example 6. Figure 7B also shows that c-maf specifically binds to the MARE (nucleotide positions -42 to -37, as claimed in claim 68) and Th2-specific footprint of the IL-4 promotor.

Therefore, the instant specification teaches the use of regulatory sequences that bind to c-maf in assays, and also specifically teaches the use of MARE sequences, *e.g.,* nucleotide positions -157 to +58, -42 to -37, and -59 to -28. In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejections of claims 68 and 69 under 35 U.S.C. §112, first paragraph.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Applicant believes no fee is due with this statement. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. HUI-021CNRCE2 from which the undersigned is authorized to draw.

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Respectfully submitted,

By _____

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